THE UNITED STATES PATENT AND TRADEMARK OFFICE
Re: Appeal to the Board of Appeals

In re the application of	) **MAIL STOP APPEAL BRIEF**
	)
HAUER et al.	) Group Art Unit: 1639
	)
Serial No. 09/674,962	) Examiner: Wessendorf
	)
Filed: November 8, 2000	)
	)

For: NOVEL PEPTIDE FRAGMENTS FOR PURIFYING PROTEINS

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1. [ ] NOTICE OF APPEAL: Applicant hereby appeals to the Board of Appeals from the decision dated _____ of the Primary Examiner finally rejecting claims ___.
2. [ ] A check in the amount of $___ is attached to cover the required extension of time fee.
3. [x] BRIEF on appeal in this application is transmitted herewith.
4. [ ] An Oral Hearing is requested.
   [ ] The Oral Hearing fee of $290.00 is enclosed.
5. [X] Fee $330.00
   [X] Enclosed
6. [X] The Commissioner is hereby authorized to charge any fees which may be further required, or credit any over payment to Account No. 11-0345. A duplicate copy of this sheet is attached.

Respectfully submitted,
KEIL & WEINKAUF

By_____
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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Honorable Comm'r. of Patents
PO Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

Sir:

This appeal is from the examiner's final office action mailed on February 12, 2004.

REAL PARTY IN INTEREST

The real party in interest is BASF Aktiengesellschaft, of Ludwigshafen, Germany. Reel/Frame 011830/0340, recorded on November 8, 2000.

RELATED APPEALS AND INTERFERENCES

To appellants' knowledge and belief, there are no interferences or other appeals which will directly affect or be directly affected by or have a bearing on the Board's decision in this application.

STATUS OF THE CLAIMS

Claims 1-18 currently are pending in the application. Claims 1-5 are rejected. Claim 6 has been allowed. Claims 7-18 have been withdrawn from consideration.

STATUS OF THE AMENDMENTS

The claims have not been amended subsequent to the final office action mailed on February 12, 2004.

SUMMARY OF THE INVENTION

The present invention relates to novel peptide fragments, fusion proteins comprising the peptide fragments, processes for preparing them, and the use of the peptide fragments. The invention also relates to a process for purifying fusion proteins and a method for detecting proteins. The invention further relates to nucleic acids which code for the peptide fragments or for the fusion proteins, and vectors which comprise the nucleic acids. It is an object of the present invention to provide tags for protein purification by immobilized metal affinity chromatography (IMAC) which make it possible to use the tags more widely and load the column material with greater density and which show a higher selectivity and thus simplify the purification.

ISSUES

Whether claims 1-4 are obvious in view of Volz et al. (Journal of Chromatography), Haymore et al. (EP 409814) and Guerinot et al. (5,846,821).

GROUPING OF CLAIMS

The claims have not been argued separately.

ARGUMENT

The following legal authorities are relied on in the following arguments in the order in which they are cited:

In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Ex parte Levengood, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).

W.L. Gore Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983).

REJECTION

Claims 1-4 are rejected under 35 USC § 103(a) as being unpatentable over Volz et al. (Journal of Chrmomatography) in view of Haymore et al. (EP 409814) and Guerinot et al. (5,846,821).

The examiner issued the obviousness rejection over Volz et al. and Guerinot et al. because the examiner believes it would have been obvious to one of ordinary skill in the art at the time the invention was made to replace Leu in the peptide fragment of Volz with a homologous amino acid, Ile with reasonable expectation that the binding property of the peptide fragment of Volz is maintained since Guerinot teaches that these residues are conservatively substituted with one another.

Applicants traverse the Examiner's obviousness rejection because applicants believe the motivation to combine Volz et al., Haymore et al. and Guerinot et al. has not been established adequately by the examiner.

To establish a *prima facie* case of obviousness, there must be some suggestion

or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Also, a statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made;" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reasons to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).

Volz et al. teach the characterization of the metal-binding domain of the ATPase-439 and ATPase-948 of *Helicobacter pylori* (Abstract and page 29, last paragraph). It was possible for Volz et al. to purify said ATPases without using an additional His-tag sequence (see page 29, Abstract, last sentence and page 37, conclusions, last sentence.) Volz et al. do not teach anything about a method using the motif HxHxxxCxxC for the purification of other proteins or fusion proteins between said motif and other protein. Since Volz et al. do not discuss a general method of using parts of the ATPase or the motif for the purification of proteins applicants do not see why the skilled worker would use part of the ATPase of the motif for the purification of proteins.

The examiner stated that since the examined claims are not method claims applicants' arguments are not commensurate in scope with the claims. However, the fact that Volz et al. do not discuss a general method of using parts of the ATPase or the motif for the purification of proteins is still relevant to whether there would be motivation to combine/modify the cited references. This is because one of ordinary skill in the art would not replace the Leu peptide fragment of Volz et al. as the examiner believes because Volz et al. because Volz et al. does not discuss a general method of using parts of the ATPase or the motif for the purification of proteins.

In addition, applicants' own studies have shown that these ATPase binding sites display a binding affinity which is too low for efficient purification of all desired proteins (specification page 2, lines 40 to 45). Applicants' sequences bind to immobilized metal ions at least 1.5 times more strongly than the *Helicobacter pylori* ATPase-439 (page 9, lines 28-32 and page 14, lines 39-46) and are therefore useful for the purification of a lot of proteins. By using the advantageous sequences, it is possible to purify proteins in a very high yield (page 14, lines 43 to 46). Nothing is mentioned about this in Volz et al. Therefore, applicants do not see why the skilled worker should consider Volz et al.

Guerinot et al. teach the discovery of a family of polypeptide, designated as metal-regulated transporter, MRP, polypeptide, which share several structural/functional properties, at least one of which is related to metal transport (see column 2, lines 24-28, claims 23 and 24). Functionally, the MRT polypeptide are capable of, for example, transporting metals, e.g., Fe, Fe(II), Cd, Co, Mn, Pb, Hg and/or Zn (see col. 2, lines 35-

37).

The MRT proteins disclosed by Guerinot et al. have four histidine rich domains (see col. 2, line 44). In Fig. 1A such a histidine rich domain is disclosed. It has the following sequence: His-Gly-His-Gly-His-Gly-His-Gly-. This protein fragment is totally different from the claimed protein fragments.

Also, the disclosure mentioned by the examiner in Guerinot et al. col. 14, line 27 is a general teaching that the amino acids Ile and Leu belong to the group of amino acids which have uncharged side chains and therefore a skilled worker would change the codon usage of a given nucleic acid sequence coding for example for Leu to the codon usage of Ile in the event he is interested in mutagenizing the said sequence without changing the activity of the enzyme encoded by the sequence. These types of changes are only possible as disclosed by Guerinot et al. in areas which are not essential for the activity of the MRP proteins (see col. 14, lines 30 to 33).

Haymore et al. teach different proteins for immobilized-metal affinity chromatography. None of the disclosed proteins (see page 4, table, lines 15 to 33) share any homology with applicants' inventive sequences. The sequences disclosed by Haymore et al. are composed of two histidine residues, one histidine residue and one aspartic acid residue. Nothing is mentioned about two histidine and two cysteine residues in combination.

Applicants remind the examiner that to imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record

convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its character. *W.L. Gore Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983).

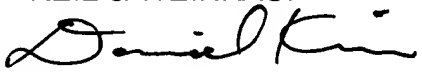
The examiner believes it must recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. This of course is true. However, applicants believe the foregoing shows that the examiner would only have arrived at the claimed invention by picking and choosing the elements and the knowledge was not within the level of ordinary skill at the time the claimed invention was made.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that reversal of the examiner's rejection of all claims is in order.

Please charge any shortage in fees due in connection with the filing of this paper, including Extension of Time fees to Deposit Account No. 11-0345. Please credit any excess fees to such deposit account.

Respectfully submitted,
KEIL & WEINKAUF



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APPENDIX

1. A peptide fragment having the general sequence

His-X^1-His-X^2-X^3-X^4-Cys-X^5-X^6-Cys (SEQ ID NO:1),

where the variables X^1 to X^6 in the sequence have the following meanings:

X^1 = an amino acid selected from the group consisting of Ala, Val, Phe, Ser, Met, Trp, Tyr, Asn, Asp or Lys and the variables X^2 to X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^2 = an amino acid selected from the group consisting of Val, Ile, Phe, Pro, Trp, Tyr, Gln, Glu or Arg and the variables X^1, X^3 to X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^3 = an amino acid selected from the group consisting of Gly, Ile, Thr, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His and the variables X^1, X^2, X^4 to X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^4 = an amino acid selected from the group consisting of Val, Phe, Pro, Cys, Met, Trp, Asn, Glu, Arg or His and the variables X^1 to X^3, X^5, X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^5 = an amino acid selected from the group consisting of Gly, Ser, Cys, Met, Trp,

Asn, Glu, Lys or Arg and the variables X^1 to X^4, X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^6 = an amino acid selected from the group consisting of Phe, Pro, Ser, Cys, Trp, Tyr or Gln and the variables X^1 to X^5 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His and

where at least one of the variables X^1 to X^6 in the sequence is, independently of one another, Gln or Asn.

2. A peptide fragment as claimed in claim 1, in which the variables X^1 to X^6 have the meanings stated in claim 1, where at least one of the variables X^1 to X^6 in the sequence is, independently of one another, Lys or Arg.

3. A peptide fragment as claimed in claim 1, in which the variables X^1 to X^6 in the sequence have the following meanings independently of one another:

X^1 = an amino acid selected from the group consisting of Ala, Val, Phe, Ser, Met, Trp, Tyr, Asn, Asp or Lys;

X^2 = an amino acid selected from the group consisting of Val, Ile, Phe, Pro, Trp, Tyr, Gln, Glu or Arg;

X^3 = an amino acid selected from the group consisting of Gly, Ile, Thr, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg or His;

X^4 = an amino acid selected from the group consisting of Val, Phe, Pro, Cys, Met,

Trp, Asn, Glu, Arg or His;

X^5 = an amino acid selected from the group consisting of Gly, Ser, Cys, Met, Trp, Asn, Glu, Lys or Arg;

X^6 = an amino acid selected from the group consisting of Phe, Pro, Ser, Cys, Trp, Tyr or Gln.

4. A peptide fragment as claimed in claim 1, in which the variables X^1 to X^6 in the sequence have the following meanings independently of one another:

X^1 = an amino acid selected from the group consisting of Phe, Ser, Asn, Asp or Lys;

X^2 = an amino acid selected from the group consisting of Val, Ile, Phe, Pro, Gln, Glu or Arg;

X^3 = an amino acid selected from the group consisting of Gly, Ile, Thr, Met, Trp, Tyr, Asn, Asp, Glu, Arg or His;

X^4 = an amino acid selected from the group consisting of Val, Phe, Cys, Met, Trp, Asn, Arg or His;

X^5 = an amino acid selected from the group consisting of Gly, Ser, Cys, Met, Asn, Glu, Lys or Arg;

X^6 = an amino acid selected from the group consisting of Phe, Ser, Cys, or Tyr.

5. A peptide fragment as claimed in claim 1 , in which the variables X^1 to X^6 in the sequence have the following meanings:

X^1 = Asn;

X^2 = Gln, Glu or Arg;

X^3 = Gly, Thr or Tyr;

X^4 = Asn or Arg;

X^5 = Gly or Lys;

X^6 = Cys.

6. A peptide fragment having the sequence

His-Gln-His-Glu-Gly-Arg-Cys-Lys-Glu-Cys (SEQ ID NO:2)

His-Asn-His-Arg-Tyr-Gly-Cys-Gly-Cys-Cys (SEQ ID NO:3)

His-Arg-His-Gly-Thr-Asn-Cys-Leu-Lys-Cys (SEQ ID NO:4)

His-Ile-His-Gln-Ser-Asn-Cys-Gln-Val-Cys (SEQ ID NO:5).

7. (withdrawn) A fusion protein comprising a protein fragment as claimed claim 1.

8. (withdrawn) A nucleic acid fragment coding for a protein fragment as claimed in claim 1.

9. (withdrawn) A nucleic acid comprising a nucleic acid fragment as claimed in claim 8.

10. (withdrawn) A nucleic acid coding for a fusion protein as claimed in claim 7.

11. (withdrawn) A vector comprising a nucleic acid fragment as claimed in claim 8.

12. (withdrawn) A process for preparing fusion proteins as claimed in claim 7, which comprises fusing a nucleic acid fragment to a gene which codes for a protein.

13. (withdrawn) A process for purifying fusion proteins as claimed in claim 7, which comprises

a) bringing liquids which contain the fusion protein into contact with

immobilized metal ions in such a way that an affinity linkage can form between the metal ions and the fusion protein,

b) removing unbound substances present in the liquid,

c) eluting the bound fusion protein by abolishing the affinity linkage by changing the liquid medium and

d) collecting the purified fusion protein.

14. (withdrawn) The use of a protein fragment as claimed in claim 1 or of a nucleic acid fragment for purifying proteins.

15. (withdrawn) A process for preparing protein fragments able to enter into a reversible affinity linkage with immobilized metal ions, which comprises carrying out the following steps:

a) preparing a nucleic acid library starting from any suitable nucleic acid sequence which codes for a protein fragment of the sequence

His-X^1-His-X^2-X^3-X^4-Cys-X^5-X^6-Cys (SEQ ID NO:11),

where the histidine and cysteine residues of the sequence are conserved in the nucleic acid library,

b) fusing the nucleic acids of the library to a reporter gene which makes it possible to detect the fusion protein encoded by the resulting nucleic acid via its binding to the immobilized metal ions and

c) selecting the nucleic acid sequences which display a reversible binding to the immobilized metal ions which is at least 1.5 times stronger than the

sequence in the natural Helicobacter pylori ATPase-439.

16. (withdrawn) A process as claimed in claim 15, wherein the egf protein from Aequoria victoria is used as reporter gene.

17. (withdrawn) A method for detecting proteins, which comprises detecting individual proteins which comprise a protein fragment as claimed in claim 1 in a protein mixture via antibodies which are directed against the protein fragment.

18. (withdrawn) The use of a protein fragment as claimed in claim 1 of a nucleic acid fragment for purifying proteins.